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TOBACCO INDUSTRY RESEARCH COMMITTEE
350 FIFTH AVENUE NEW YORK 1, N. Y.

Application For Research Grant

Date: April 19, 1956

1. Name of Investigator: Adrian M. Ostfeld, M.D.

2. Title: Assistant Professor of Preventive Medicine

3. Institution & Address: University of Illinois College of Medicine
840 South Wood Street
Chicago, Illinois

4. Project or Subject: A biomicroscopic assay of bulbar conjunctival vascular reactivity in hypertension employing topical and parenteral pharmacologic agents.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

The arterioles, capillaries and venules of the bulbar conjunctival vessels may be readily examined by means of a Poser Ophthalmic slit lamp at a magnification of 47.5X and appropriate photographs made. 1 The effects of pharmacologic agents may be assayed either by preparing them in an isotonic phosphate buffer at a pH of 7.4 and applying them directly on the bulbar conjunctivae or after parenteral administration. When one eye is treated and the other serves as control, transient changes in systemic hemodynamics and variations in absorption rates of different agents do not prejudice experimental results. These technics will be employed in the study of the following problems.

The studies of Goldenberg on blood pressure responses [2], Lee on bulbar conjunctival minute vessels [3], and Griesman [4] on nail fold capillaries have all concurred in the observation that small blood vessels of hypertensive patients are more reactive to epinephrine and nor-epinephrine than those of normotensives. Since the latter agent is probably the true sympathetic vasoconstrictor substances, hyper-reactivity to nor-epinephrine may play an important role in the genesis and maintenance of the hypertensive state.

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Detailed Plan of Procedure - Cont'd.

Such hyperreactivity in hypertension may be determined by one or more of the following mechanisms: 1) an hydraulic and mechanical effect; i.e. a vessel already partly constricted may more readily constrict further with blood viscosity assuming greater importance in small diameter tubes, 2) the presence of a circulating agent or agents which potentiates nor-epinephrine effects 3) a true vascular smooth muscle hyperreactivity to nor-epinephrine.

The following proposed studies would help to determine which of the above mechanisms is relevant. 1) In hypertensive and normotensive subjects, the diameter of representative arterioles will be measured by micrometer and the threshold to topical nor-epinephrine determined. (Threshold is defined as the least concentration of nor-epinephrine which predictably closes metarteriolar sphincters and blanches capillaries.) The arterioles would then be doubled in diameter by means of topical applications on separate occasions of three structurally and chemically unrelated vasodilators; histamine, acetylcholine combined with pilocarpine, isopropyl nor-epinephrine. If vasodilation decreases nor-epinephrine reactivity (i.e. raises threshold) the inference is that arteriolar diameter per se, and therefore mechanical and hydraulic factors largely determine this vascular response. If diameter changes do not alter reactivity, the other possible mechanisms thereby receive support.

2) In both hypertensive and normotensive subjects, the effects of other topically applied vasoconstrictors, namely nicotine and pitressin would be studied. If there is hyperreactivity to these agents in hypertensive subjects or if nor-epinephrine thresholds are lowered by pre-treatment with these vasoconstrictors, then the effects of nor-epinephrine are not specific and again a mechanical and hydraulic factor appears most relevant. Again, if the converse is true, the other theses become more likely.

3) An opportunity is herein afforded to study the effects of topical and injected nicotine on the minute vessel appearance and reactivity in normotensive and in hypertensive subjects and to assess a possible relevance of nicotine (and less directly of smoking) in the genesis and progression of hypertensive vascular disease.

4) The vascular appearance and reactivity of the bulbar conjunctivae in normal subjects transiently made hypertensive by intravenous nor-epinephrine will be studied, and a comparison made with the same vascular properties in hypertensive subjects. If no differences are manifest then it is highly unlikely that the vascular smooth muscle behaves differently in hypertensive subjects.

While none of these experiments by itself would serve conclusively to establish the mechanism of nor-epinephrine hyperreactivity in hypertension, reliable evidence to support one or another mechanism would be obtained.

(see next page for references)
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1. Ostfeld, et. al., HEADACHE AND HYDRATION, A.M.A. Archives of Internal Medicine, August 1955, Vol. 96, pp. 142-152

2. Goldenberg, et. al., HEMODYNAMIC RESPONSE OF MAN TO NOR-EPINEPHRINE AND EPINEPHRINE AND ITS RELATION TO THE PROBLEM OF HYPERTENSION, Am. J. Med., Vol. 5, p. 792, 1948

3. Lee and Holze, PERIPHERAL VASCULAR HEMODYNAMICS IN THE BULBAR CONJUNCTIVA OF SUBJECTS WITH HYPERTENSIVE VASCULAR DISEASE, The Journal of Clinical Investigation, Vol. XXX, No. 6, pp. 539-546, June, 1951

4. Greisman, THE REACTION OF THE CAPILLARY BED OF THE NAILFOLD TO CONTINUOUS INTRAVENOUS INFUSION OF LEVO-NOR-EPINEPHRINE IN PATIENTS WITH NORMAL BLOOD PRESSURE AND WITH ESSENTIAL HYPERTENSION, The Journal of Clinical Investigation, Vol. XXXIII, p. 975, July, 1954.

5. Von Euler, THE NATURE OF ADRENERGIC NERVE MEDIATORS, Pharm. Rev., Sept. 1951, p. 247.

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6. Budget Plan:

Salaries	$4000.00
Expendable Supplies	500.00
Permanent Equipment	500.00
Overhead 12 6/8	1300.00
Other	0.00
Total	$6300.00

7. Anticipated Duration of Work: 2 years

8. Facilities and Staff Available: 1. A research bed in the Research and Education Hospital affiliated with the Medical School. 2. The patients load and facilities of the Hypertension Clinic and other OPD Clinics of the hospital. 3. A laboratory in the hospital prepared in anticipation of this study. 4. Adrian M. Ostfeld, M.D. Assistant Professor of Preventive Medicine. 5. A technician and assistance from the resident level medical house staff.

9. Additional Requirements: None

10. Additional Information (Including relation of work to other projects and other sources of supply):

No other sources of supply.
This project grew out of a two-year study of bulbar conjunctival vascular reactivity in headache in the laboratories of Dr. Harold G. Wolff, Professor of Medicine (Neurology), New York Hospital-Cornell Medical Center.

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/s/
Signature Adrian M. Ostfeld
Director of Project

Business Officer of the Institution

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Salaries	$24,000.00
Expendable supplies	200.00
Permanent equipment	500.00
Overhead	0.0
Other	
Total	$24,700.00

5. Anticipated Duration of Work: 3 years

6. Facilities and Aid Available: A research unit at the Roosevelt Hospital Corporation Hospital to be established shortly by Dr. [illegible] of the Department of Medicine, Columbia University College of Physicians and Surgeons. Dr. [illegible] is Director of the Department of Medicine at Roosevelt Hospital and Professor of Medicine at Columbia University College of Physicians and Surgeons. Dr. [illegible] is Director of the Department of Medicine at Columbia University College of Physicians and Surgeons and Attending Physician at Presbyterian Hospital. Dr. [illegible] is Director of the Department of Medicine at Columbia University College of Physicians and Surgeons and Attending Physician at Presbyterian Hospital. Dr. [illegible] is Director of the Department of Medicine at Columbia University College of Physicians and Surgeons and Attending Physician at Presbyterian Hospital.

7. Additional Requirements: None

8. Additional information: (Include any other sources of support for this project and any other projects to which you will devote time.)

All other sources of support for this project and any other projects to which you will devote time.

Laboratory facilities and clinical material for this project will be provided by the Department of Medicine, Columbia University College of Physicians and Surgeons and Presbyterian Hospital.

Signature of Principal Investigator

Director of Project

Business Officer of the Institution

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